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FINAL SCIENTIFIC REPORT BY THE UNIVERSITY OF COLORADO
TO THE OFFICE OF NAVAL RESEARCH, DEPARTMENT OF THE NAVY
(N6ori-131, TASK ORDER #1, UNIVERSITY OF COLORADO)
(Period of Task - June 15, 1946 to December 31, 1952)

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TITLE OF PROJECT: The Phenomena of Diffusion Respiration Including a Study of the Physiology and Therapeutics of High Concentrations of Carbon Dioxide

Twenty-two communications have appeared in the literature, one has been accepted for publication and six papers will shortly be written on the subjects comprised in this task order. A bibliography of these papers is appended and they are referred to in this report by number.

Paper No. 1, 2 and 3 of the bibliography represent work done in this laboratory before ONR financial support was received. Paper No. 1 and Paper No. 3, an abstract, deal in a preliminary way with diffusion respiration. Paper No. 2 amplified Paper No. 1 by showing that dogs can be maintained in respiratory arrest by diffusion respiration for 45 minutes and gave certain details concerning the concentration of alveolar oxygen and carbon dioxide that developed in the course of 45 minutes of apnea. At the request of the Editor Paper No. 1 has been reprinted in the January-February, 1953 issue of The Journal of Small Animal Medicine. The Editor has indicated that he plans to reprint a series of our papers on diffusion respiration in this Journal.

Papers No. 4 and 9 deal with the alveolar gases, the venous and arterial blood gases and the venous and arterial pH during diffusion respiration. In Paper No. 4 it was shown that, during apnea under diffusion respiration, the alveolar concentration of carbon dioxide rises about 1% a minute i.e. from a control average of 6.2% to an average level of 54.7% in the course of 45 minutes of

apnea. Within 30 minutes after the resumption of breathing the alveolar carbon dioxide level falls to normal. All 12 dogs involved in these experiments were resuscitated. One died 96 hours after the experiment. In Paper No. 9 the following data are reported:

"During the first thirty minutes of diffusion respiration the oxygen content of arterial and venous abdominal blood was well maintained. Between the thirtieth and forty-fifth minute of respiratory arrest there was a progressive fall in the oxygen content of arterial and venous blood. After the initiation of lung ventilation the arterial and venous oxygen content reached their control values within fifteen minutes. There was, however, a temporary secondary fall in the oxygen content of venous blood at the thirtieth minute after diffusion.

During the forty-five minutes of respiratory arrest there was a progressive rise in carbon dioxide content and a concomitant rise in the hydrogen ion concentration of arterial and venous abdominal blood. The average pH values at the forty-fifth minute of respiratory arrest were 6.72 for arterial blood and 6.84 for venous. After sixty minutes of lung ventilation the carbon dioxide content and hydrogen ion concentration of both arterial and venous blood had approximated their control values.

The carbon dioxide content of the arterial blood during diffusion respiration became, in every experiment, greater than that of the venous blood and concomitantly the hydrogen ion concentration of the arterial blood became higher than that of the venous blood. Following resumption of lung ventilation the normal relationships between these values reappeared within fifteen minutes."

Paper No. 6 is an abstract giving some information concerning the "hemoglobin-oxygen" pump.

Paper No. 7, an abstract, is a preliminary study of the changes in kidney function before, during and after diffusion respiration. Paper No. 22 provides

more complete information concerning the anuria that occurs during apnea under diffusion respiration. It was shown that a pharmacological block of the renal nerves greatly delays the appearance of anuria.

An additional Paper No. 27 is to be published on this subject and a manuscript will be sent to ONR as soon as it has been prepared. This paper will contain data showing that hypercapnia plays an important role in the production of the anuria of diffusion respiration. Reasons, however, will be given to justify the belief that other factors are also operating to produce anuria.

In Paper 25, an abstract, work is reported in which respiratory arrest was induced in 65 dogs by the intracisternal injection of procaine hydrochloride. Anuria or oliguria developed in all dogs during the ensuing diffusion respiration. The anuria or oliguria usually occurred promptly after the onset of the apnea. The importance of this work is that it shows that anuria occurs in the absence of profound thiopental sodium anesthesia. In all previous work a profound thiopental sodium anesthesia was present during the anuria. A detailed paper will be prepared shortly (No. 32 in the bibliography). Similarly, it has been shown that when apnea is induced by curare and certain other neuro-muscular blocking agents i.e. in the absence of profound thiopental sodium anesthesia, an anuria develops. A Paper No. 30 will be prepared on this subject.

In Paper No. 8, an abstract and in Paper No. 17 it is shown that, with the institution of diffusion respiration under thiopental sodium anesthesia, the cortical electrical activity is reduced, and periods of "black-out" appear which increase in length until finally there is complete cortical electrical silence. These changes rapidly reverse to normal with the resumption of spontaneous breathing.

In Papers No. 10 and 14 data concerning the behavior of the heart rate, blood pressure and electrocardiogram in dogs during diffusion respiration are presented.

It is shown that these aspects of the circulation are not seriously affected by severe hypercapnia. In fact, the circulation under diffusion respiration is remarkably stable considering the strain to which the animal is subjected.

Papers No. 5 and 15 are review articles and summarize the information obtained on the physiology of diffusion respiration up to October 1948.

Paper No. 11, an abstract, and Paper No. 19 deal with the effect of diffusion respiration and of high concentrations of CO_2 on the C.S.F. pressure of dogs anesthetized with thiopental sodium. In this work the C.S.F. pressure was measured by means of a strain gauge which provided a more accurate determination of the fluctuations in pressure than was obtained by previous workers through the use of the water manometer. It was shown that hypercapnia, whether brought about by failure of the apneic animal to exhale or by the inhalation of CO_2, produces a very rapid increase in the C.S.F. pressure at the cisterna magna which reaches a maximum within 5 minutes. This may explain the harmful effect of morphine in cranial injury. The use of morphine in such cases by depressing respiration causes hypercapnia and a consequent rise in the C.S.F. pressure. The use of a strain gauge enabled us to observe a phenomenon which had been hypothesized previously but not seen i.e. that fluctuations in the arterial pressure are mirrored by concomitant changes in the C.S.F. pressure.

Paper No. 12, an abstract, and Paper No. 18 deal with the tolerance of the dog anesthetized by thiopental sodium to high concentrations of carbon dioxide. It was found that an underlying light thiopental sodium anesthesia protects the dog from convulsions and tachycardia during a 45-minute exposure to 10, 20, 30 and 40% CO_2 in O_2. The only significant change in the electrocardiogram observed during the respiratory acidosis was an increase in the amplitude of the T wave. Data were given concerning the effect of the various concentrations of CO_2 in O_2 on the venous pH.

In Paper No. 21, an abstract, and in Paper No. 26 the effect of diffusion respiration and of the inhalation of high concentrations of CO_2 on plasma volume, thiocyanata space, blood cells and oxygen capacity has been discussed. It was reported that severe hypercarbia whether brought about by diffusion respiration or by the inhalation of CO_2 in O_2 resulted in a marked decrease in plasma volume, an irregular increase in thiocyanata space and substantial increases in the red cell count, red cell volume, and oxygen capacity of venous blood. There was no consistent change in either the white or differential count.

Paper No. 29 is in preparation. It will discuss the changes in the composition of the plasma occurring during diffusion respiration and during the first 24 hours of the recovery period. Data will be presented showing that during diffusion respiration the principal changes in the electrolytes of the plasma are increases in bicarbonate and inorganic phosphate. Other disturbances occurring are moderate increases in urea and amino acid nitrogen. There is also a two to three-fold increase in glucose. During the succeeding 24 hours all constituents investigated returned to normal values.

In Paper No. 16, an abstract, and in Paper No. 23 the effects of diffusion respiration and of prolonged inhalation of carbon dioxide in oxygen on the human have been discussed with especial reference to the electroencephalogram. It was reported that, as in the dog, diffusion respiration or the inhalation of high concentrations of CO_2 produced periodic suppressions in the EEG and that these suppressions progressed to complete electrical silence as the exposure of the subject was prolonged. It was attempted in these studies to determine if diffusion respiration or the prolonged inhalation of CO_2 had a therapeutic effect on patients having schizophrenia. Some tendency to at least a temporary improvement of such patients was noted, but the results were not sufficiently clear cut to justify a clinical conclusion. One patient subjected to diffusion respiration died some hours

after he had been resuscitated to the point of spontaneous respiration.

In Paper No. 20, an abstract, and in Paper No. 24 the effect of respiratory acidosis on the plasma levels of thiopental and on the depth of thiopental sodium anesthesia was discussed. Paper No. 24 has been accepted for publication in Current Researches and will appear shortly. It will be shown that when dogs in second plane thiopental sodium anesthesia are caused to inhale a 40% CO_2 in O_2 mixture the plasma thiopental falls rapidly. Data will also be presented showing that as the percentage of CO_2 in the inhaled mixture is increased the amount of thiopental sodium required to maintain a dog in second plane anesthesia is proportionately decreased, and that the effect of CO_2 here is so powerful as to suggest that CO_2 potentiates the anesthetic effect of thiopental sodium.

In Paper No. 28, now in preparation, the relationship between oxygen pressure and the survival-time of dogs in diffusion respiration will be discussed. The following table is a resume of the data to be presented:

Partial Pressure of Oxygen	No. of Experiments	Average Survival-Time
330 mm. of Hg.	5	35 minutes
430 mm. of Hg.	5	44 minutes
530 mm. of Hg.	5	58 minutes
630 mm. of Hg.	5	69 minutes
730 mm. of Hg.	5	87 minutes
830 mm. of Hg.	5	73 minutes
930 mm. of Hg.	7	86 minutes
1030 mm. of Hg.	7	86 minutes

It will be noted that as the partial pressure of oxygen is reduced stepwise from 730 mm. of Hg., there is a corresponding reduction in the survival-time of dogs under diffusion respiration. On the other hand, when the partial pressure of oxygen is increased above 730 mm. of Hg., there is no corresponding increase in the

average survival-time. EKG records were taken at intervals throughout each experiment, and the paper will contain an analysis of these observations.

Paper No. 13, an abstract, and Paper No. 31 are concerned with the effect of the inhalation of 20% of CO_2 in O_2 upon the antibiotic activity of penicillin and aureomycin against pneumococcus Type 3 infections in mice. Paper No. 31 is in preparation. Data will be presented showing that mice infected with a specific strain of pneumococcus Type 3 and treated with penicillin plus the inhalation of 20% CO_2 in O_2 exhibited a longer survival-time than controls given penicillin alone. When aureomycin was the antibiotic the inhalation of 20% CO_2 in O_2 produced no essential change in survival-time.

SUGGESTIONS FOR FURTHER WORK

Much remains to be done in the field of diffusion respiration. The changes in renal physiology occurring during diffusion respiration and during the inhalation of high concentrations of CO_2 are particularly interesting and should be investigated further. It is certain that the elucidation of the more intimate mechanisms involved in this anuria will be a substantial contribution to our knowledge of kidney function. Further, the fact that anuria develops promptly on the cessation of respiratory movements and disappears promptly on the resumption of respiratory movements, indicates that there is here a useful investigational tool for the study of certain aspects of renal physiology particularly anuria.

We have demonstrated many times that the "hemoglobin-oxygen" pump produces during apnea a mass movement inward of the atmosphere including not only oxygen but whatever other gas may be present such as nitrogen and carbon monoxide. We have not studied this phase of the problem extensively, but there can be little doubt that during an apnea under conditions favorable to diffusion respiration whatever gases (including anesthetics) which are present in the atmosphere will be sucked inwards to the alveoli. We have shown for instance, that an animal in

respiratory arrest under diffusion respiration can be quickly killed by simply introducing carbon monoxide into the ambient atmosphere. The demonstration that gas poisoning can occur in the absence of breathing has significance wherever men are exposed to toxic gases. This phase of the problem may be of special interest to the Department of the Navy.

An application is pending before the United States Public Health Service for financial support to enable us to conduct further investigations in the general field of diffusion respiration and of the physiology of carbon dioxide.

Respectfully submitted,

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March 25, 1953

PUBLICATIONS ON DIFFUSION RESPIRATION AND THE PHYSIOLOGICAL EFFECTS OF HIGH CONCENTRATIONS OF CARBON DIOXIDE

A. Publications on Diffusion Respiration Prior to Beginning of O.N.R. Financial Sponsorship

1. DIFFUSION RESPIRATION IN THE DOG UNDER PENTOTHAL SODIUM. William B. Draper and Richard W. Whitehead. Anesthesiology, Vol. 5, pp. 262-273, 1944.

2. STUDIES ON DIFFUSION RESPIRATION. II. SURVIVAL OF THE DOG FOLLOWING A PROLONGED PERIOD OF RESPIRATORY ARREST. L. W. Roth, R. W. Whitehead and W. B. Draper. Anesthesiology, Vol. 8, pp. 294-302, May, 1947.

3. DIFFUSION RESPIRATION IN THE DOG UNDER PENTOTHAL SODIUM. William B. Draper and Richard W. Whitehead. Federation Proceedings, Vol. 3, pp. 70, March, 1944.

PUBLICATIONS ON DIFFUSION RESPIRATION AND THE PHYSIOLOGICAL EFFECTS OF HIGH CONCENTRATIONS OF CARBON DIOXIDE

B. Publications Dealing With Investigations Carried Out Under O.N.R. Financial Sponsorship

4. STUDIES ON DIFFUSION RESPIRATION: III. ALVEOLAR GASES AND VENOUS BLOOD pH OF DOGS DURING DIFFUSION RESPIRATION. William B. Draper, Richard W. Whitehead and Joseph N. Spencer, with the technical assistance of David L. G. Beshore and Thomas M. Parry. Anesthesiology, Vol. 8, No. 5, pp. 524-533, September, 1947.

5. THE PHENOMENON OF DIFFUSION RESPIRATION. William B. Draper, Richard W. Whitehead, Joseph N. Spencer, Thomas M. Parry and Eli S. Goldensohn, Symposium on Military Physiology, The National Military Establishment, Research and Development Board, Washington 25, D.C., Prepared by: Department of the Army, Chemical Corps, Office of the Surgeon General, Digest Series No. 4, p. 123, 02 61/1 4-6 December, 1947. (No reprints available)

6. STUDIES ON DIFFUSION RESPIRATION: V. THE HEMOGLOBIN-OXYGEN PUMP. Joseph N. Spencer, William B. Draper, Thomas M. Parry and Richard W. Whitehead. Federation Proceedings, Vol. 7, No. 1, p. 119, March, 1948.

7. STUDIES ON DIFFUSION RESPIRATION: VI. CHANGES IN KIDNEY FUNCTION IN DOGS. R. W. Whitehead, D. L. G. Beshore, W. B. Draper, J. N. Spencer and T. M. Parry. Federation Proceedings, Vol. 7, No. 1, p. 264, March, 1948.

8. STUDIES ON DIFFUSION RESPIRATION: VII. ELECTRICAL CORTICAL ACTIVITY IN DOGS. Eli S. Goldensohn, Ewald W. Busse, Joseph N. Spencer, William B. Draper and Richard W. Whitehead. Federation Proceedings, Vol. 7, No. 1, p. 223, March, 1948.

9. STUDIES ON DIFFUSION RESPIRATION. IV. THE OXYGEN AND CARBON DIOXIDE CONTENT AND THE HYDROGEN ION CONCENTRATION OF ARTERIAL AND VENOUS ABDOMINAL BLOOD OF DOGS DURING DIFFUSION RESPIRATION. Richard W. Whitehead, Joseph N. Spencer, Thomas M. Parry and William B. Draper. Anesthesiology, Vol. 10, pp. 54-60, 1949.

10. STUDIES ON DIFFUSION RESPIRATION. VIII. CHANGES IN HEART RATE, BLOOD PRESSURE AND ELECTROCARDIOGRAM IN DOGS DURING DIFFUSION RESPIRATION. T. M. Parry (by invitation), J. N. Spencer (by invitation), R. W. Whitehead and W. B. Draper. Amer. J. Physiol. 155, p. 459, December, 1948.

11. PRESSURE RESPONSES OF THE CEREBROSPINAL FLUID TO DIFFUSION RESPIRATION AND CARBON DIOXIDE INHALATION. Joseph N. Spencer (by invitation), Eli S. Goldensohn (by invitation), Richard W. Whitehead, Robert F. Grover (by invitation) and William B. Draper. Federation Proceedings, 8, p. 149, 1949.

PUBLICATIONS ON DIFFUSION RESPIRATION AND THE PHYSIOLOGICAL EFFECTS OF HIGH CONCENTRATIONS OF CARBON DIOXIDE

B. Publications Dealing With Investigations Carried Out Under O.N.R. Financial Sponsorship

12. THE EFFECTS OF INHALATION OF HIGH CONCENTRATIONS OF CARBON DIOXIDE. T. M. Parry (by invitation), Joseph N. Spencer (by invitation), William B. Draper, Richard W. Whitehead and Robert L. Arends (by invitation). Federation Proceedings, Vol. 8, p. 323, 1949.

13. POTENTIATION BY MEANS OF CARBON DIOXIDE OF THE ACTION OF PENICILLIN AGAINST PNEUMOCOCCUS INFECTION. Richard W. Whitehead, J. Howard Williamson (by invitation), William E. Clapper (by invitation), Joseph N. Spencer (by invitation) and William B. Draper. Federation Proceedings, Vol. 8, p. 347, 1949.

14. STUDIES ON DIFFUSION RESPIRATION. VIII. CHANGES IN HEART RATE, BLOOD PRESSURE AND ELECTROCARDIOGRAM IN DOGS DURING DIFFUSION RESPIRATION. T. M. Parry, J. N. Spencer, R. W. Whitehead and W. B. Draper. Anesthesiology, Vol. 10, pp. 615-620, September, 1949.

15. THE PHENOMENON OF DIFFUSION RESPIRATION. William B. Draper and Richard W. Whitehead. Current Researches in Anesthesia and Analgesia, Vol. 28, pp. 307-318, November-December, 1949.

16. EFFECTS OF INHALATION OF 20% AND 25% CARBON DIOXIDE IN OXYGEN DURING PENTOTHAL SODIUM ANESTHESIA IN THE HUMAN. Thomas M. Parry, R. W. Whitehead, W. B. Draper, J. N. Spencer and E. S. Goldensohn. J. of Pharm. & Exper. Thera., Vol. 98, pp. 24-25, January, 1950. (No reprints available).

17. STUDIES ON DIFFUSION RESPIRATION. VII. THE CORTICAL ELECTRICAL ACTIVITY OF DOGS. Eli S. Goldensohn, Ewald W. Busse, Joseph N. Spencer, William B. Draper and Richard W. Whitehead. J. of Electroencephalography and Clinical Neurophysiology, Vol. 2, No. 1, p. 33, 1950.

18. THE TOLERANCE OF THE DOG UNDER THIOPENTAL SODIUM ANESTHESIA TO HIGH CONCENTRATIONS OF CARBON DIOXIDE. Joseph N. Spencer, Thomas M. Parry, Richard W. Whitehead and William B. Draper. J. of Pharm. and Exper. Thera., Vol. 98, No. 4, p. 366, April, 1950.

19. STUDIES ON DIFFUSION RESPIRATION. IX. THE EFFECT OF DIFFUSION RESPIRATION AND HIGH CONCENTRATIONS OF CO_2 ON THE CEREBROSPINAL FLUID PRESSURE OF ANESTHETIZED DOGS. Eli S. Goldensohn, Richard W. Whitehead, Thomas M. Parry, Joseph N. Spencer, Robert F. Grover and William B. Draper. Am. J. Physiol., Vol. 165, No. 2, pp. 334-340, May, 1951.

20. THE INFLUENCE OF RESPIRATORY ACIDOSIS ON THE PLASMA LEVELS OF THIOPENTAL SODIUM. Chalmers J. Rayburn (by invitation), Richard W. Whitehead and William B. Draper. Fed. Proc., Vol. 10, March, 1951, p. 331 (No reprints available).

PUBLICATIONS ON DIFFUSION RESPIRATION AND THE PHYSIOLOGICAL EFFECTS OF HIGH CONCENTRATIONS OF CARBON DIOXIDE

B. Publications Dealing With Investigations Carried Out Under O.N.R. Financial Sponsorship

21. PLASMA VOLUME CHANGES PRODUCED BY INHALATION OF CO_2. J. H. Holmes, T. M. Parry, W. B. Draper and R. W. Whitehead. J. of Clinical Investigation, Vol. 29, p. 823, 1950 (No reprints available).

22. A STUDY OF ANURIA OCCURRING DURING APNEA UNDER DIFFUSION RESPIRATION. F. A. Kopecky, C. J. Rayburn, R. W. Whitehead and W. B. Draper. Am. J. Physiol., Vol. 168, No. 1, pp. 131-137, January, 1952.

23. ALTERATION OF CEREBRAL FUNCTION IN MAN PRODUCED BY DIFFUSION RESPIRATION AND PROLONGED INHALATION OF CARBON DIOXIDE. Ewald W. Busse, Thomas M. Parry, Eli S. Goldensohn, Richard W. Whitehead and William B. Draper. Diseases of the Nervous System, Vol. 13, No. 2, p. 35, February, 1952.

24. THE INFLUENCE OF RESPIRATORY ACIDOSIS ON THE PIASMA LEVELS OF THIOPENTAL AND ON THE DEPTH OF ANESTHESIA. Chalmers J. Rayburn, Richard W. Whitehead and William B. Draper with the technical assistance of S. Foster, W. B. Dodgson and J. E. Stone. (Delivered by W. B. Draper at Virginia Beach, September 25, 1952. To appear in Current Researches.

25. CHANGES IN URINE SECRETION DURING DIFFUSION RESPIRATION FOLLOWING APNEA INDUCED BY INTRACISTERNAL INJECTION OF PROCAINE. Richard L. Irwin, Joseph E. Stone, William B. Draper and Richard W. Whitehead. Federation Proceedings. Abstract 1096, Vol. 12, p. 332, 1953.

26. EFFECT OF DIFFUSION RESPIRATION AND OF INHALATION OF HIGH CONCENTRATIONS OF CO_2 ON PLASMA VOLUME, THIOCYANATE SPACE, BLOOD CELLS AND O_2 CAPACITY. Robert L. Arends, Chalmers J. Rayburn, William B. Draper and Richard W. Whitehead. Am. J. Physiol., Vol. 171, pp. 507-512, No. 2, November, 1952.

PUBLICATIONS ON DIFFUSION RESPIRATION AND THE PHYSIOLOGICAL EFFECTS OF HIGH CONCENTRATIONS OF CARBON DIOXIDE

C. Investigations Which Were Completed Under O.N.R. Financial Sponsorship But Not, As Yet, Written Up For Publication

27. EFFECT OF INHALATION OF HIGH CONCENTRATIONS OF CO_2 ON THE SECRETION OF URINE.

28. EFFECT OF VARIOUS ALTITUDES ON THE SURVIVAL-TIME OF DOGS UNDER DIFFUSION RESPIRATION.

29. EFFECT OF DIFFUSION RESPIRATION ON THE COMPOSITION OF THE PLASMA.

30. DIFFUSION RESPIRATION UNDER NEURO-MUSCULAR BLOCKING AGENTS.

31. THE EFFECT OF RESPIRATORY ACIDOSIS ON THE EFFICIENCY OF CERTAIN ANTIBIOTICS.

32. DIFFUSION RESPIRATION IN APNEA INDUCED BY INJECTIONS OF PROCAINE HCl INTRACISTERNALLY.